

Attorney Docket No: 23546-07724US

Client Ref: RTS-0333

USSN: 10/008,789

REMARKS**STATUS OF THE CLAIMS**

Claims 1, 2, 4-10, 12-15, and 19-20 were pending in this application. Claims 1 and 19 have been amended. Following entry of the amendments, claims 1, 2, 4-10, 12-15, and 19-20 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claim 1 has been amended to add the language "targeted to nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6" and delete the language "targeted to the 5'-untranslated region, the start codon region, the coding region, the stop codon region, or the 3'-untranslated region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6, with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3." Support for this amendment can be found throughout the specification as filed, e.g., page 82, Table 1, and data regarding compounds comprising SEQ ID NOS:15-67.

Claim 19 has been amended to add the language "differentially inhibits by at least 41% the expression of a first variant of thyroid hormone receptor interactor 6, TRIP6-I (SEQ ID NO:3) relative to a second variant of thyroid hormone receptor interactor 6, TRIP6-II (SEQ ID NO:11)" and deleting the language regarding one or more variants. Support for this amendment can be found throughout the specification as filed, e.g., Example 17 on page 84 of the specification, where embodiments of the compounds claimed by Claim 19 are disclosed, e.g., SEQ ID NOS:16 17, and 18. SEQ ID NOS:16-18 specifically hybridize with and differentially inhibit, e.g., inhibit to a greater degree, the expression of a first variant, TRIP6-I (SEQ ID NO:3) relative to the expression of a second variant, TRIP6-II (SEQ ID NO:11).

The amendments to the claims therefore add no new matter and entry is respectfully requested.

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REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Applicant acknowledges the Examiner's withdrawal of the rejection of claim 19 under 112, second paragraph.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 19 was rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Examiner stated that the specification "...does not provide sufficient description that would allow one of skill in the art to use human thyroid hormone receptor interactor 6 (SEQ ID NO:3) or a variant of human thyroid hormone receptor interactor 6 (SEQ ID NO: 11) to predict the structures of antisense compounds complementary to target sites or "active sites" of thyroid hormone receptor interactor 6 isolated from other sources, including all polymorphic, allelic and splice variants of this mRNA ... fails to describe the complete structure of a representative number of species of the claimed genus."

Without agreeing with the Examiner's position, Applicant has amended claim 19 to recite the SEQ ID NOS of two variants of thyroid hormone receptor interactor 6. Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 102(B)

Claims 1, 2, 12, 14, 19, and 20 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by the following art:

Murthy et al (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667), disclosing a primer with reverse complementarity to nucleobases 169-148 of SEQ ID NO:3;

Zhao et al (Gene Expression, 1999 Vol. 8:207-217), disclosing an upstream adaptor primer corresponding to the 5' end of human Trip6; and

Yi et al. (Genomics, 1998 Vol. 49:314-316), disclosing an oligonucleotide primer that with reverse complementarity to nucleobases 1689-1665 of SEQ ID NO:3.

Applicant respectfully disagrees with the Examiner's contention that any of the compounds disclosed in the cited art necessarily possess the characteristic of Applicant's claimed product, e.g., the characteristic of hybridizing to and inhibiting the expression of thyroid hormone receptor interactor 6. Applicant incorporates herein the arguments made in the

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05/24/04 Response against the similar rejection of the claims over a different oligonucleotide disclosed in Murthy et al.

However, in order to expedite prosecution, Applicant has amended claim 1 to recite a target region that excludes the regions complementary to the compounds disclosed in the cited art, rendering moot the pending rejections. Withdrawal of this basis of rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C 102(E)

Claims 1, 2, 4-10, 12-15, 19, and 20 were rejected under 35 U.S.C. 102(e) as allegedly anticipated by Cowser et al. [U.S. Patent No. 6,492,173] disclosing an antisense oligonucleotide (see SEQ ID NO:49). The Examiner stated that SEQ ID NO:49 of Cowser has "... reverse complementary to bases 1518-1533 of SEQ ID NO:3 of the instant invention with two mismatches (see attached sequence alignments)." Applicant points out that SEQ ID NO:49 of Cowser is not complementary to bases 1518-1533 of SEQ ID NO:3 but rather has reverse identity with bases 1518-1533 of SEQ ID NO:3. Accordingly, SEQ ID NO:49 of Cowser could not hybridize to bases 1518-1533 of SEQ ID NO:3 of the instant invention. Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1, 2, 19, and 20 were again rejected under 35 U.S.C. 103(a) as allegedly obvious over Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667) in view of Milligan et al. (Journal of Medicinal Chemistry, 1993 Vol. 36:1923-1937). Claims 4-10 and 12-15 were again rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667) in view of Milligan et al. (Journal of Medicinal Chemistry, 1993 Vol. 36:1923-1937) as applied to claims 1 and 2 above, and further in view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Applicant rebuts the Examiner's arguments as drawn to the claims as amended herein. As recited in amended Claim 1, Applicant's invention is a compound targeted to nucleobases 259

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through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6. The remaining claims are dependent on claim 1 and therefore include this element.

Three requirements must be met for a prima facie case of obviousness. First, the combination of prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required.

I. The cited combination of prior art references does not teach all of the elements of the claims as amended herein.

Claim 1 as amended herein claims compounds targeted to nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6. Nowhere does the combination of references cited by the Examiner teach or suggest the target site recited in claim 1 as amended herein. Accordingly, the combination cannot render the claims obvious.

II. The cited combination of prior art at best provides a generalized incentive insufficient to render obvious the claimed species.

The combination of art cited by the Examiner also fails to render obvious the rejected claims because the references at best contain a generalized incentive to make antisense molecules against thyroid hormone receptor interactor 6, based on the discovery and characterization of the thyroid hormone receptor interactor 6 protein as taught by Murthy et al and a generalized teaching to make antisense targeted to a "causative gene" as taught by Milligan et al. The cited combination of art provides no teaching or suggestion to make the specific antisense compounds claimed, e.g., compounds directed to the target site as recited in amended claim 1. Baracchini et al. and Fritz et al. do not remedy these deficiencies. The combination therefore fails to make out a prima facie case of obviousness because "a general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel* 51 F.3d at 1559, 34 USPQ2d at 1216.

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Applicant notes that the number of potential inhibitory compounds targeted to thyroid hormone receptor interactor 6 encompasses a vast number of possibilities. As the Federal Circuit held in *In re Baird*, disclosure of a broad genus does not necessarily render obvious each compound within its scope. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Thus, even though the prior art included a polynucleotide sequence encoding thyroid hormone receptor interactor 6 from which potential inhibitory compounds, e.g., antisense oligonucleotides, could be designed, the specific compounds instantly claimed (e.g., those targeted to the recited target region and that specifically hybridize and inhibit expression) still would not be obvious given the failure of the prior art to teach or suggest these specific compounds claimed.

III. Inhibitory oligonucleotide design at the time of the invention was not sufficiently predictable from gene to gene to provide a generic reasonable expectation of success.

Modifying or combining art to make out a prima facie case of obviousness also requires that the prior art provide an ordinarily skilled artisan working at the time of the invention with a reasonable expectation of success in making the claimed invention. MPEP § 2143.02. Applicant submits that the cited references fail to provide a reasonable expectation of success because the cited references fail to provide direction as to which of many possible choices of thyroid hormone receptor interactor 6 compounds was likely to be successful. As such, the cited combination at best makes the claimed invention "obvious to try." It does not render it obvious. *See In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

In response to Applicant's similar argument made in the 05/24/04 Response, the Examiner has pointed to 10 patents issued to the Assignee that published before Applicant's filing date, stating that "each and every patent contains anywhere from a few to many oligonucleotides that inhibit target gene expression." Applicant respectfully points out that none of the 10 patents contain oligonucleotides that inhibit thyroid hormone receptor interactor 6 gene expression, much less target nucleobases 259 through 1586 of the coding region of a nucleic acid molecule (SEQ ID NO:3) encoding thyroid hormone receptor interactor 6. Each patent discloses

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oligonucleotides targeted to a different target gene; none of these 10 patents provide direction as to which of the many possible choices was likely to be successful when targeting nucleobases 259 through 1586 of the coding region of a nucleic acid molecule of SEQ ID NO:3 encoding thyroid hormone receptor interactor 6.

In view of the amendments to the claims and the above arguments, Applicant requests withdrawal of this basis of rejection of the claims.

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CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
BENNETT ET AL

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